Feeling Lightheaded: The Role of Cerebral Blood Flow

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Objective: The main aims of this study were a) to investigate the relationship between lightheadedness and cerebral blood flow velocity (CBFv) during hyperventilation-induced hypocapnia, and b) to investigate whether and why the relationship between lightheadedness and CBFv may change after several episodes of this sensation. **Methods:** Three hypocapnic and three normocapnic overbreathing trials were administered in a semirandomized order to healthy participants ($N = 33$). Each type of breathing trial was consistently paired with one odor. Afterward, participants were presented each odor once in two spontaneous breathing and in two normocapnic overbreathing trials. CBFv in the right middle cerebral artery was measured by transcranial Doppler ultrasonography (TCD). Also breathing behavior and self-reported lightheadedness were measured continuously. Each trial was followed by a symptom checklist. **Results:** Self-reported lightheadedness was closely related to changes in CBFv in the hypocapnic overbreathing trials. During the subsequent normocapnic trials, however, participants experienced more lightheadedness and "feeling unreal" to the odor that had previously been paired with hyperventilation-induced hypocapnia. These complaints were not accompanied by changes in end-tidal CO_2 nor in CBFv. **Conclusions:** The results show that lightheadedness is associated with changes in CBFv but that after a few episodes, the underlying mechanism for this symptom may shift to perceptual-cognitive processes. These findings may help to understand why lightheadedness occurs during emotional distress and panic. In addition, altered cerebral blood flow is unlikely to play a primary precipitating role in recurrent symptoms of lightheadedness. **Key words:** lightheadedness, pseudoneurological complaints, cerebral blood flow, hyperventilation, conditioning, transcranial Doppler.

Abbreviations: **PNC** = pseudoneurological complaints; **IEI** = idiopathic environmental illness; **CBF** = cerebral blood flow; **CBFv** = cerebral blood flow velocity; **CS** = conditioned stimulus; **US** = unconditional stimulus; **TCD** = Transcranial Doppler ultrasonography; **MCA** = middle cerebral artery; **VAS** = Visual Analogue Scale; **Vi** = inspiratory volume; **$FetCO_2$** = fractional end-tidal CO_2; **Vm** = intensity weighted mean blood flow velocity in the right middle cerebral artery.

INTRODUCTION

The term pseudoneurological complaints (PNCs) is often used in psychosomatic medicine to refer to complaints such as lightheadedness or dizziness, concentration problems, feelings of dissociation/derealization, numbness, weakness, difficulties concentrating, poor memory, and fatigue without a clear medical explanation, although the set of symptoms is not clearly defined (i.e., the term PNC has been used inconsistently to refer to [subsets of] a variety of somatic and cognitive complaints [1–3]). They have been documented to relate to stress and anxiety (1,4). In addition, PNCs show a strong overlap with symptoms seen in idiopathic environmental illness (IEI)/multiple chemical sensitivity, posttraumatic stress disorder, panic disorder, and several "functional syndromes" such as chronic fatigue syndrome (3–9). In this study, we focus on processes underlying lightheadedness, a cardinal symptom of hyperventilation which itself has been frequently reported in IEI and panic disorder (5,10–15). Lightheadedness is assumed to be caused by cerebral ischemia (a decrease in cerebral blood flow [CBF]) as a result of hyperventilation-induced hypocapnia (16). However, the relationship between changes in CBF and changes in lightheadedness during hyperventilation has not been investigated in detail. In addition, previous work of our group has demonstrated that repeated symptom episodes in association with specific cues produces learning that may alter the relationship between a symptom and its underlying physiological cause. For example, in a differential conditioning paradigm, harmless odors (conditioned stimuli [CSs]) were mixed with CO_2-enriched air (unconditional stimulus [US]) during a number of breathing trials and subsequently presented alone (17). This resulted in elevated symptom reports during the presentation of the odor previously paired with the CO_2 inhalation, indicating a learning effect.

Hyperventilation has been discredited as an explanation for a wide variety of symptoms that were attributed to it after it was found that such symptoms did not temporally coincide with hypocapnic episodes (18,19). However, the critical role of hyperventilation may be restored by this learning account when assuming that repeated symptom episodes may change the relationship between a symptom and its underlying cause. Earlier, we administered hyperventilation-induced hypocapnia as a US inducing symptoms including lightheadedness, whereas specific but harmless odor cues were added to the breathing circuit as CSs (5). Afterward, participants felt more unreal and reported lightheadedness quicker in response to the specific odor that had been presented together with the hypocapnic episode. This was not accompanied by any concomitant differences in end-tidal CO_2 (5). Voluntary hyperventilation can be seen as a laboratory analogue for real-life hyperventilation episodes, which are highly prevalent in anxiety and nonclinical states of stress (20–23). In that respect, these hypocapnic challenges may have a wider relevance than hypercapnic ones. In our laboratory model, odors were used as CSs, and voluntary hyperventilation was a US. However, in real life, hyperventilation may be elicited by stress and anxiety, so that cues associated with these condi-

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[1]Concentrations were based on a pilot study in which 15 participants who did not participate in the main study rated the intensity of several concentrations of both odors.

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tions may function as CSs and induce symptoms on subsequent occasions.

An important remaining question is what mechanism underlies learned lightheadedness. Two explanations have been put forward (5). First, symptom perception processes could account for the experience of the learned complaint. Several models of symptom perception and medically unexplained symptoms assign a significant role to memory representations in the generation of a perceptual experience (24,25). Second, the presence of learned lightheadedness can be related to a conditioned cerebral vasoconstriction/cerebral ischemia, even in the absence of hypocapnia. Several observations make the latter speculation viable: a) Pavlovian conditioning of vascular responses has been reported in several studies (26–28), b) altered CBF reactions to blood level of CO_2 changes have been found in panic disorder patients (29–31), and c) cerebral arterioles have been shown to be innervated by sympathetic neurons, and although the influence of sympathetic activation on CBF has been the topic of discussion (32), sympathetic activation has been shown to induce cerebral vasoconstriction (33–35).

The aims of this study were to investigate the relationship between CBF velocity (CBFv) and lightheadedness during periods of hyperventilation and to investigate whether learned lightheadedness in response to chemical cues is accompanied by decreases in CBFv. Transcranial Doppler ultrasonography (TCD) was used to measure CBFv in the right middle cerebral artery (MCA). TCD is a validated technique to measure mean and regional CBFv (36–41), which has often been used to assess reactivity to changes in CO_2 (42,43). We hypothesized that a) lightheadedness is strongly related with CBF during hyperventilation in the first place, and b) after a few learning episodes, odors previously paired with hypocapnia (CS+) would induce more lightheadedness compared with odors previously paired with normocapnia (CS−) without concomitant differences in end-tidal CO_2. Regarding CBF, we explored whether the acquired lightheadedness would be related to a decreased CBFv during CS+ in a test phase as a result of conditioned cerebral vasoconstriction.

METHODS

Participants

Thirty-six university students, recruited using a mailing list, volunteered to participate in return for 12€. Exclusion criteria were self-report of: alcohol consumption 6 hours before the experiment, disease, (history of) psychological or psychiatric disorder, (history of) migraine, and medication use (except for contraceptives). Two participants were excluded because of technical issues (capnograph failure and insufficient Doppler signal power, respectively) and one because of failure to comply with the hyperventilation instructions. This resulted in a study sample of 33 participants (29 women, mean age 18.6 years). The experiment was approved by the Ethics Committees of the Department of Psychology and of the Faculty of Medical Sciences. The data were collected between December 2007 and February 2008.

Materials

Materials and measures used were partly the same as used in a previous study of this group (5). Only the most important and new features are discussed in this study.

Self-Report Measures

During each trial, participants continuously rated lightheadedness on a vertical computerized Visual Analog Scale (VAS, 0–100) using a keyboard. Other complaints were assessed after each trial using an adapted version of the Checklist for Psychosomatic Symptoms (5,44), consisting of complaints belonging to one of eight subsets: anxiety, dizziness, cardiac, gastrointestinal, paresthesia, respiratory, dummy, and unclassified complaints, together with two added hyperventilation complaints (lightheadedness and feeling unreal). Dummy complaints were four sensations that are rarely associated with hyperventilation (nasal congestion, joint pain, low back pain, and burning eyes) to control for response biases.

Apparatus

The setup of the breathing circuit, apparatus calibration, and parameter extraction were predominantly based on a previous study of our group (5). To this breathing circuit, a bacterial filter (Microgard, Viasys Heathcare) was added, which was placed on the mask to avoid sample line occlusion by condensation from expired air. In addition, a second capnograph was added to the original breathing circuit (Capnoguard $ETCO_2$ Monitor, Novametrix Medical Systems Inc., USA). This capnograph sampled expired air from the expiratory tube and was used in the normocapnic overbreathing trials because the administration of CO_2 influenced the online estimation of end-tidal CO_2 with air sampled near the mask. Both capnographs were calibrated before each experimental session using a calibration gas containing 7.5% CO_2; the pneumotachograph was calibrated using a calibrated syringe (Calibration Pump 1L, Viasys Healthcare GmbH, Germany). The CO_2 and flow signal (transformed offline into a volume signal) were processed with a Labmaster card (Labmaster DPCI, Scientific Solutions) at a sampling rate of 100 Hz and stored on personal computer using Affect (Affect 4 [45]).The following parameters were calculated for each breathing cycle: respiratory rate (breathing frequency, breaths/min), inspiratory volume (Vi, ml), inspiratory drive (ml/s), and fractional end-tidal CO_2 ($FetCO_2$, %). Odors (0.8% ammonia, 7.4% acetic acid)[1] were dispersed at a rate of 3 liters/min using a nebulizer (Sidestream, Respironics) connected to the mask. A mixture of 35% CO_2 (21% O_2 and 44% N_2) was administered at a variable flow rate into the inspiratory tube during normocapnic breathing trials (see later).

A TCD (Doppler box, DWL) measured CBFv (sampled at 100 Hz) in the right MCA with a 2-MHz probe. One limitation is that CBFv is measured instead of CBF, making its reliability dependent on the constancy of the diameter of the insonated artery. In support of this assumption, several studies have shown that the MCA remains relatively constant during hyper and hypocapnia (46–48). Second, because the measure depends on the angle between the probe and the insonated artery (49), the probe was fixed using a headband device (Marc 600, Spencer Technologies), and only relative values were used. Specific software (QL software, DWL) was used to calculate intensity weighted mean velocity (Vm).

Procedure

On arrival, participants were screened for the exclusion criteria. Next, they read a cover story explaining that this study investigated the effects of cleaning products for air conditioning systems on several complaints. The text explained that participants would receive one of two possible air mixtures in each trial and that the air mixtures could possibly induce complaints. It was assured that the mixtures were not harmful and that eventual complaints would be of low intensity and transient. Participants consenting to participate provided written informed consent. The use of the computerized VAS was then illustrated explaining that "0" represented no lightheadedness and "100" the maximum lightheadedness one could experience. Finally, subjects were told that in most trials they would have to breathe as deeply as possible on the rhythm of a metronome. This was demonstrated by the experimenter. After the instructions, the right MCA was insonated through the right temporal window just above the zygomatic arch using a standard technique (50), at a range of depth between 45 and 55 mm. The Doppler signal was optimized by increasing the sample depth in a stepwise manner and changing the angle of the probe. Once the optimal signal was obtained, the probe was secured onto the headband.

The experiment contained several overbreathing and spontaneous breathing trials. Each trial consisted of 10 seconds of nose breathing, followed by 80 seconds of mouth breathing. This was done to ensure odor perception. A five-minute recovery, during which participants completed the symptom checklist, followed each trial. In the overbreathing trials, participants were instructed to breathe as deeply as possible at the pace of a metronome, targeted at 30 breaths/min. During the trials, the experimenter instructed the participants over an intercom system to breathe as deeply as possible and to follow the metronome as closely as possible.

The experiment used a typical differential conditioning paradigm, consisting of a training and test phase (Figure 1). The training phase consisted of three hypocapnic overbreathing trials and three normocapnic overbreathing trials, which were presented in semirandomized order with no more than two consecutive trials of the same type. One odor was paired with the hypocapnic overbreathing trials (CS+); the other with the normocapnic overbreathing trials (CS−). Additionally, two on-screen labels were used to increase CS+/CS− differentiation ("zeumhydride" and "nialinecitraat"). During CS−, 35% CO_2-enriched air was added into the inspiratory tube at an experimenter-controlled flow rate to maintain normocapnia. The normocapnic target value of $FetCO_2$ was determined individually during a baseline trial before training. The pairing of the odors and labels with either a CS+ or a CS− trial was randomized over participants. The test phase consisted of two blocks in randomized order: a block consisting of two spontaneous breathing trials and a block with two normocapnic overbreathing trials. Within each block, the first trial was always presented with a CS− odor-label pair and the second trial with CS+.

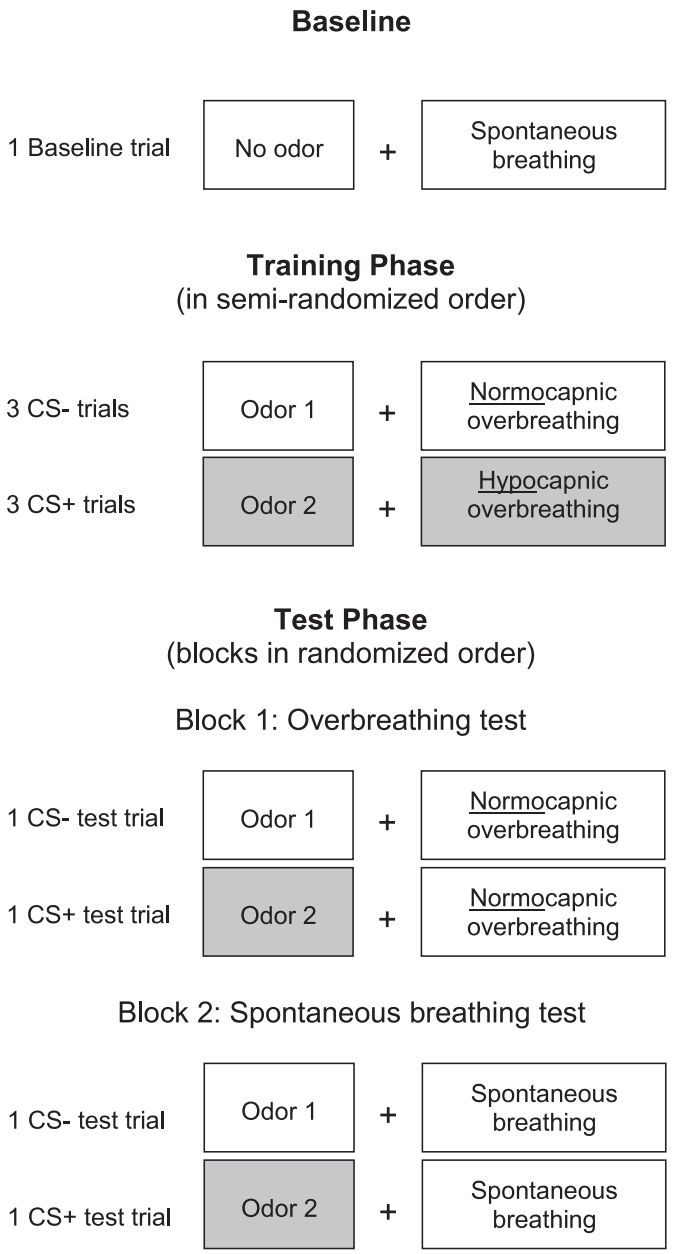

Figure 1. Schematic representation of the study design.

Data Reduction and Analysis

Three parameters were calculated based on the online measure of lightheadedness: the time elapsed before the first lightheadedness (TEBL), calculated as the time before participants rated lightheadedness; the maximal intensity of lightheadedness rated by participants during a trial; and the mean intensity of lightheadedness after the first rating.

The posttrial items lightheadedness and feeling unreal were analyzed separately. For the other symptom items of the posttrial questionnaire, analysis was done by subgroup. Before respiratory parameter calculation, irregular and shallow breaths not reaching an end-tidal alveolar plateau (<1% of all breaths) were rejected. Afterward, averages of each respiratory parameter for each 10-second interval were calculated with each breath weighted for its relative time occupied in the interval. For Vm, a percentage change to baseline was calculated and averaged for each 10-second interval in the same manner as the breathing parameters. For Vm and online lightheadedness, 5-second intervals were also calculated, which were used to determine the correlation between both measures in training and test CS+ trials.

Data from training and test phases were analyzed separately. The six overbreathing trials of the training phase were analyzed in a CS+ odor (ammonia, acetic acid) × CS (CS+, CS−) × trial (first, second, third) × interval (1–8, for breathing and CBFv data) repeated measures analysis of variance. The two overbreathing and spontaneous breathing test trials were each analyzed in a CS+ odor (ammonia, acetic acid) × CS (CS+, CS−) × interval (1–8, for breathing and CBF data) analysis of variance. All statistics will be reported for time elapsed before the first lightheadedness, mean, and maximum intensity of lightheadedness. The description of the results will primarily focus on significant patterns, and the data are presented in the tables. Greenhouse-Geisser corrections were applied when appropriate. Furthermore, we computed f^2 effect sizes. Cohen (51) described values of 0.02, 0.15, and 0.35 as small, medium, and large, respectively.

RESULTS

Training

Online Lightheadedness

Compared with CS−, participants did not experience lightheadedness quicker during CS+ (Table 1). Participants did experience lightheadedness earlier in the first trial compared with the third (Tukey honestly significant difference [HSD] test $p = .013$) and tended to have lightheadedness earlier in the first compared with the second trial (Tukey HSD test $p = .057$). The maximum lightheadedness was higher during CS+ compared with CS− and was also higher in the third trial compared with the first (Tukey HSD test $p = .022$). The mean lightheadedness was higher during CS+ compared with the CS− training trials. In addition, the mean lightheadedness tended to be higher in the third trial compared with the first ($F(2,62) = 2.95$, $\epsilon = 0.94$, $p = .063$, $f^2 = 0.07$, Tukey HSD test $p = .061$).

Complaints

For the training trials, participants reported more lightheadedness and "feeling unreal" during CS+ compared with CS− trials (Table 1). For lightheadedness, the main effect of trial

TABLE 1. Means (Standard Deviations) and Significant Effects of Complaints During Training ($N = 33$)

Measure	Baseline	Trial 1		Trial 2		Trial 3		Statistics		
		CS+	CS−	CS+	CS−	CS+	CS−	Significant Effects	F (p)	f^2
LH online										
TEBL	n/a (n/a)	54.78 (28.91)	57.12 (35.45)	46.24 (19.91)	44.83 (37.16)	42.35 (21.95)	43.46 (33.89)	TRIAL	4.90 (.015)	0.17
Mean	0 (0)	14.05 (11.75)	6.50 (9.30)	15.08 (9.30)	6.86 (7.33)	17.95 (14.28)	8.48 (8.98)	CS	22.15 (<.001)	0.82
Max	0 (0)	22.76 (20.31)	8.15 (10.73)	26.94 (19.26)	8.33 (8.20)	30.27 (26.55)	10.45 (9.37)	CS	29.92 (<.001)	2.19
								TRIAL	3.77 (.031)	0.11
Complaints										
Lightheadedness	1.09 (0.29)	2.49 (0.87)	1.48 (0.48)	2.97 (0.73)	1.45 (0.51)	3.03 (1.02)	1.55 (0.51)	CS	110.86 (<.001)	5.21
								TRIAL	5.44 (.011)	0.19
								CS × TRIAL	4.95 (.014)	0.16
Feeling unreal	1.12 (0.33)	1.64 (0.82)	1.36 (0.65)	1.70 (0.91)	1.45 (0.75)	1.67 (0.95)	1.48 (0.75)	CS	5.45 (.026)	0.15
Anxiety	1.34 (0.38)	1.53 (0.57)	1.31 (0.46)	1.52 (0.65)	1.20 (0.28)	1.57 (0.71)	1.22 (0.37)	CS	15.65 (<.001)	1.26
Cardiac	1.06 (0.15)	1.42 (0.43)	1.17 (0.29)	1.46 (0.56)	1.25 (0.35)	1.66 (0.65)	1.27 (0.41)	CS	22.89 (<.001)	1.54
								TRIAL	6.27 (.005)	0.38
								CS × TRIAL	3.65 (.037)	0.12
Dizziness	1.03 (0.10)	1.49 (0.34)	1.09 (0.17)	1.54 (0.34)	1.17 (0.25)	1.75 (0.51)	1.17 (0.24)	CS	100.81 (<.001)	4.25
								TRIAL	7.65 (.002)	0.43
								CS × TRIAL	5.83 (.006)	0.19
Dummy	1.06 (0.13)	1.14 (0.23)	1.10 (0.16)	1.08 (0.15)	1.08 (0.13)	1.13 (0.22)	1.08 (0.15)	—	—	—
Gastrointestinal	1.02 (0.07)	1.10 (0.20)	1.05 (0.18)	1.10 (0.18)	1.11 (0.31)	1.09 (0.21)	1.08 (0.20)	—	—	—
Respiratory	1.18 (0.28)	1.73 (0.53)	1.45 (0.36)	1.76 (0.66)	1.44 (0.40)	1.85 (0.68)	1.52 (0.40)	CS	13.43 (<.001)	1.05
Paresthesia	1.02 (0.07)	1.38 (0.70)	1.05 (0.21)	1.36 (0.57)	1.08 (0.20)	1.42 (0.66)	1.12 (0.25)	CS	10.82 (.003)	1.67
Unclassified	1.09 (0.11)	1.22 (0.23)	1.12 (0.16)	1.28 (0.26)	1.18 (0.27)	1.37 (0.38)	1.23 (0.29)	CS	20.68 (<.001)	4.25
								TRIAL	12.45 (<.001)	4.25

LH online = online lightheadedness; TEBL = time elapsed before lightheadedness; mean = mean lightheadedness; max = maximum rated lightheadedness; n/a = not applicable; CS+ = odor paired with hypocapnia; CS− = odor paired with normocapnia; significant effects: $\alpha = 0.05$; CS = conditioned stimulus (CS+–CS−); TRIAL = trial (1–3).
df for F statistics: CS = 1:31, TRIAL = 2:62, CS × TRIAL = 2:62.

was also significant and the CS × trial interaction. Further analysis of this interaction showed that participants rated less lightheadedness in the first CS+ trial compared with the following two CS+ trials (Tukey HSD test, all p values $<$ .001); no such differences were found for CS− trials.

Except for the dummy (nasal congestion, joint pain, low back pain, and burning eyes) and gastrointestinal symptoms, all scores on the symptom subgroups were higher for CS+ training trials compared with CS−. Participants also rated less unclassified complaints in the first trial compared with the other trials (Tukey HSD test, Trial 2: $p = .012$; Trial 3: $p <$ .001). For cardiac symptoms and dizziness, the main effect of trial and the CS × trial interaction were significant. Further analysis of these interactions showed an increase in dizziness and cardiac symptoms in the third compared with the first two CS+ trials (Tukey HSD test, dizziness: all p values $<$ .001; cardiac: Trial 1: $p = .002$, Trial 2: $p <$ .001); no differences were found for CS− trials.

Breathing

As a result of the manipulation, significant effects were observed of CS, interval, and CS × interval for $FetCO_2$ during training, all in the expected direction (Table 2). In addition, $FetCO_2$ was lower in the last two CS+ trials compared with the first (Tukey HSD test, $p <$ .001), whereas no such decrease was observed for CS− trials. Finally, the trial × interval interaction also reached significance. Further analysis of this interaction showed that, for all intervals except for the last two, $FetCO_2$ was lower in the first trial compared with the second trial (Tukey HSD, interval 4: $p = .007$, interval 5: $p =$ .005, all other intervals: $p <$ .001) and the third (Tukey HSD, all p values $<$ 0.001) trials. Although $FetCO_2$ was lower during CS− compared with baseline, this pattern of results indicates a successful within subject control for hypocapnic overbreathing in the normocapnic overbreathing trials.

In line with the $FetCO_2$ decrease over trials, participants breathed deeper during the last two trials compared with the first (Tukey HSD test all p values $<$ .001). Furthermore, inspiratory volume increased during the course of the trial but only in the first two trials (Trial 1 linear trend: $t(31) = 6.58$, $p <$ .001; Trial 2 linear trend: $t(31) = 2.71$, $p = .011$).

Cerebral Blood Flow

The Vm results largely paralleled those of $FetCO_2$. Significant results in the expected direction were found for CS, interval, and CS × interval (Table 2). In addition, the trial main effect was significant and the CS × trial interaction. Tukey comparisons indicate that Vm was higher in the first CS+ trial compared with the following CS+ trials (all p values $<$ .001). Finally, the trial × interval interaction also reached significance. Compared with the other trials, Vm decreased slower in the first trial, which is indicated by a significant difference in Tukey contrasts for the first three intervals of the first trial compared with same intervals of the second and third trial (Tukey HSD test p values $<$ .001). The within-subject correlation between lightheadedness and Vm during the trials was high and overall significant (mean: −0.64, standard deviation [SD]: 0.17, significant in 90% of the cases).

Overbreathing Test Trials

Online Lightheadedness

Participants tended to experience lightheadedness sooner during the CS+ test trial compared with CS− ($F(1,31) =$ 3.97, $p = .055$, $f^2 = 0.13$) (Table 3). Furthermore, during CS+, the maximum rated lightheadedness was significantly higher. No differences were found between CS+ and CS− in mean lightheadedness.

Complaints

A significant learning effect was found for lightheadedness and dizziness (Table 3). Participants also tended to rate more anxiety in the CS+ trial ($F(1,31) = 3.39$, $p = .075$, $f^2 =$ 0.11). No significant differences were found for the other symptom subscales.

Breathing

For $FetCO_2$, interval reached significance, indicating that $FetCO_2$ did not remain constant (Table 3). Further analysis of this effect does not reveal a linear decrease in $FetCO_2$ (linear trend: $t(31) = 0.87$, $p = .39$). There was, however, no significant main difference between the CS+ and CS− trial nor an interaction between CS and interval.

Breathing frequency tended to be lower in CS+ trials ($F(1,31) = 3.62$, $p = .066$, $f^2 = 0.04$), although the difference was minimal. Participants also breathed deeper during CS+ trials. For inspiratory volume, the effect of interval tended to be significant ($F(7,217) = 2.23$, $\epsilon = 0.58$, $p = .068$, $f^2 =$ 0.09). Further analysis of this effect showed no linear trend ($t(31) = 0.88$, $p = .388$), only a difference between the first and fifth interval (Tukey HSD, $p = .020$).

Cerebral Blood Flow

The changes in Vm parallel those of $FetCO_2$: only the effect of interval reached significance. Further analysis of this effect showed a significant linear increase in Vm (linear trend: $t(31) = 6.19$, $p <$ .001) (Table 3). The within-subject correlation between lightheadedness and Vm did not reach significance in any participant (mean: 0.04, SD: 0.24).

Spontaneous Breathing Test Trials

Online Lightheadedness

Participants experienced lightheadedness earlier during CS+ compared with the CS− trial (Table 3). However, no significant differences were found in mean and maximum rated lightheadedness.

Complaints

A significant learning effect was found for lightheadedness and feeling unreal (Table 3). Furthermore, participants scored higher in the CS+ trials on the anxiety and cardiac subscales.

TABLE 2. Means (Standard Deviations) and Significant Effects of Respiration and CBF Velocity During Training ($N = 33$)

Measure	Baseline	Trial 1		Trial 2		Trial 3		Statistics		
		CS+	CS−	CS+	CS−	CS+	CS−	Significant Effects	F (p)	f^2
Respiration										
$FetCO_2$	4.42 (0.56)	2.57 (0.39)	4.09 (0.43)	2.28 (0.33)	4.11 (0.37)	2.21 (0.27)	4.10 (0.33)	CS	1086.21 (<.001)	98.04
								INT	27.14 (<.001)	0.58
								TRIAL	16.75 (<.001)	0.71
								CS × INT	86.91 (<.001)	1.97
								CS × TRIAL	22.29 (<.001)	0.85
								INT × TRIAL	3.46 (.003)	0.11
Vi	698.94 (377.82)	1902.17 (551.53)	1801.13 (594.60)	2060.84 (545.72)	2046.99 (536.87)	2146.31 (548.96)	2114.18 (524.85)	INT	16.61 (<.001)	0.40
								TRIAL	25.32 (<.001)	2.08
								INT × TRIAL	9.90 (<.001)	0.24
Freq	15.86 (4.17)	29.96 (1.17)	29.88 (1.16)	29.80 (0.69)	29.98 (0.76)	29.86 (1.08)	29.84 (0.98)	—	—	—
CBF										
Vm	0 (0)	−35.78 (11.80)	−15.79 (14.43)	−40.95 (9.65)	−16.38 (12.17)	−41.57 (9.97)	−16.26 (12.45)	CS	229.87 (<.001)	35.56
								INT	45.47 (<.001)	2.61
								TRIAL	5.75 (<.001)	0.53
								CS × INT	107.36 (<.001)	3.20
								CS × TRIAL	11.72 (<.001)	0.38
								INT × TRIAL	11.27 (<.001)	0.38

$FetCO_2$ = fractional end-tidal CO_2; Vi = inspiratory volume; freq = breathing frequency; CBF = cerebral blood flow; Vm = percentage change mean velocity; CS+ = odor paired with hypocapnia; CS− = odor paired with normocapnia; significant effects: $\alpha = 0.05$; CS = conditioned stimulus (CS+–CS−); INT = Interval (1–8); TRIAL = trial (1–3).
df for F statistics: CS = 1:31, INT = 7:217, TRIAL = 2:62, CS × INT = 7:217, CS × TRIAL = 2:62, INT × TRIAL = 14:434, CS × INT × TRIAL = 14:434.

TABLE 3. Means (Standard Deviations) and Significant Effects of Complaints, Respiration, and CBF Velocity During Test ($N = 33$)

Measure	Overbreathing Test			Spontaneous Breathing Test		
	CS+	CS−	Statistics (F, p, f^2)	CS+	CS−	Statistics (F, p, f^2)
LH-online						
TEBL	41.18 (37.58)	54.65 (33.14)	—	42.93 (38.69)	60.21 (35.23)	CS (5.87,.021,0.19)
Mean	11.42 (11.44)	8.15 (9.97)	—	7.01 (8.43)	6.85 (8.45)	—
Max	18.55 (20.68)	10.76 (12.31)	CS (5.33,.028,0.13)	11.06 (14.32)	8.27 (8.96)	—
Complaints						
Lightheadedness	2.21 (0.93)	1.61 (0.66)	CS (18.86,<.001,0.61)	2.00 (0.97)	1.55 (0.67)	CS (12.02,.002,0.39)
Feeling unreal	1.58 (0.97)	1.45 (0.79)	—	1.39 (0.66)	1.15 (0.57)	CS (5.39,.027,0.17)
Anxiety	1.39 (0.57)	1.29 (0.59)	—	1.28 (0.55)	1.13 (0.25)	CS (4.77,.037,0.15)
Cardiac	1.39 (0.46)	1.36 (0.48)	—	1.30 (0.39)	1.18 (0.31)	CS (11.26,.002,0.36)
Dizziness	1.37 (0.45)	1.23 (0.44)	CS (7.97,.008,0.26)	1.26 (0.38)	1.15 (0.28)	—
Dummy	1.13 (0.23)	1.13 (0.19)	—	1.17 (0.25)	1.13 (0.18)	—
Gastrointestinal	1.14 (0.25)	1.15 (0.34)	—	1.10 (0.25)	1.08 (0.23)	—
Respiratory	1.65 (0.60)	1.48 (0.53)	—	1.36 (0.49)	1.13 (0.23)	—
Paresthesia	1.19 (0.42)	1.18 (0.40)	—	1.14 (0.33)	1.12 (0.25)	—
Unclassified	1.31 (0.35)	1.27 (0.34)	—	1.24 (0.35)	1.22 (0.31)	—
Respiration						
$FetCO_2$	4.11 (0.34)	4.08 (0.37)	INT (3.80,.005,0.13)	3.66 (0.49)	3.75 (0.52)	INT (14,59,<.001,0.71)
Vi	2223.92 (613.54)	2130.96 (565.76)	CS (6.37,.017,0.21)	744.22 (299.60)	753.90 (317.36)	—
Freq	29.39 (1.58)	29.71 (1.39)	—	18.82 (5.04)	18.73 (4.36)	—
CBF						
Vm	−17.71 (10.77)	−18.07 (12.59)	INT (20.07,<.001,1.16)	−14.42 (13.01)	−13.70 (12.59)	INT (7.95,<.001,0.45)

LH-online = online lightheadedness; TEBL = time elapsed before lightheadedness; Mean = mean lightheadedness; Max = maximum rated lightheadedness; $FetCO_2$ = fractional end-tidal CO_2; Vi = inspiratory volume; freq = breathing frequency; CBF = cerebral blood flow; Vm = percentage change mean velocity; CS+ = odor previously paired with hypocapnia; CS− = odor previously paired with normocapnia; statistics: $\alpha = 0.05$; CS = conditioned stimulus (CS+–CS−); INT = interval (1–8).
df for *F* statistics: CS = 1:31, INT = 7:217.

Breathing

$FetCO_2$ decreased during trials (linear trend: $t(31) = -5.11$, $p < .001$) (Table 3). Furthermore, $FetCO_2$ tended to be lower during CS+ compared with CS− ($F(1,31) = 3.20$, $p = .084$, $f^2 = 0.18$). Apart from $FetCO_2$, no significant effects were found on breathing parameters during the spontaneous breathing trials.

Cerebral Blood Flow

Vm decreased during trials (linear trend: $t(31) = -2.90$, $p = .007$) (Table 3). The correlation between lightheadedness and Vm did not reach significance in any participant (mean: 0.00, SD: 0.21).

DISCUSSION

The main aims of this study were to investigate the relationship between CBFv and lightheadedness during hyperventilation and to investigate the processes underlying learned lightheadedness, namely whether it was accompanied by conditioned changes in CBFv. To investigate this, we used a differential learning paradigm with hypocapnic overbreathing as US and normocapnic overbreathing as a within-subject control. Diluted ammonia and acetic acid served as CSs, together with on-screen labels of fictitious chemicals. In this paradigm, we measured breathing behavior and used TCD to measure CBFv in the right MCA. Our findings showed a lower $FetCO_2$ during hypocapnic overventilation compared with the normocapnic trials. Although $FetCO_2$ was lower than baseline during the normocapnic training trials, it was substantially higher than the levels that are generally reported as the limit below which complaints such as lightheadedness occur (around 2.8% $FetCO_2$ [52]), indicating a successful normocapnic control. This resulted in significant differences in CBFv and in complaints: CBFv was lower, and participants rated more lightheadedness during CS+ training trials compared with CS−. Participants also rated all symptom subscales higher for the CS+ compared with CS− trials, except for dummy and gastrointestinal complaints. In addition, regarding the first aim of our study, we found evidence for an overall strong (linear) relationship between lightheadedness and CBFv during hypocapnic overventilation.

In the subsequent test phase, several learning effects were observed. First, a learning effect was found on the online and the posttrial ratings of lightheadedness in the normocapnic overbreathing test. In the spontaneous breathing test, a similar effect occurred for the posttrial questionnaire, and participants rated lightheadedness sooner during the CS+ trial on the online scale. Second, learning effects were also observed on other complaint subscales, i.e., dizziness in the overbreathing test, and anxiety and cardiac complaints, and "feeling unreal" in the spontaneous breathing test.

These results indicate that lightheadedness (and other self-reported symptoms) can be acquired after a few learning trials, which documents the robustness of the findings of Van Diest

et al. (5) and corroborates them by showing that learning processes did not only influence the time of onset but also the experienced intensity. Although the intensity of acquired lightheadedness was mild, it is important to note that it took only three learning trials and that also the US (hypocapnia) was relatively mild. Our specific operationalization with hyperventilation-induced hypocapnia is potentially important because (1) it explains the inconsistent relationship between typical hyperventilation-related complaints and hypocapnia (which has been used to discard the role of hyperventilation altogether [5,18,19]), and (2) it can function as a laboratory analogue for real-life hyperventilation as a result of stress or anxiety. In the latter case, stress/anxiety may trigger hyperventilation as a US, whereas cues related to stress/anxiety and the context may become CSs for symptoms on subsequent occasions.

Although participants breathed deeper during CS+ in the overbreathing test, the learning effects on complaints were not paralleled by decreases in $FetCO_2$ nor CBFv. In contrast to acquisition, the increased lightheadedness during CS+ was not related to any changes in CBFv. These results indicate that the complaints emerged in the absence of the physiological cause that initially had caused them, favoring symptom perception processes as an explanation, which is in line with a previous study (53). In that study, a distraction task was used during the training phase of a differential odor-CO_2 conditioning paradigm. Learned complaints were modulated by the attention manipulation during the training phase and were unrelated to actual physiological responses during the test phase, indicating that learned complaints are based on activated information in memory. Obviously, repeated experiences of complaints in a particular context lead to the development of memory representations, which can subsequently be triggered by associated cues and bias the interoceptive experience of the body (see also Refs. 24, 25, and 54–56).

In conclusion, the results of this study demonstrate a strong relationship between CBF and lightheadedness during hyperventilation. However, this relationship may change across a few symptom episodes: lightheadedness became unrelated to physiological changes in $FetCO_2$ or CBFv, suggesting that its emergence became dependent on perceptual-cognitive processes or in other words, "medically unexplained." Our findings underline the value of a perceptual-cognitive learning model for lightheadedness. Clinical studies are needed to document whether this learning account may explain part of the symptoms in several pathologies such as IEI, posttraumatic stress disorder, panic disorder, and several "functional syndromes."

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